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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,785	01/04/2002	Hidemi Saito	04853.0087	1823

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EXAMINER	
GALVEZ, JAMES JASON	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,785	SAITO ET AL.	
	Examiner	Art Unit	
	J. Jason Galvez	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-22,24-29 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-22, 24-29 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

5.00

DETAILED ACTION

Response to Amendment

The amendment filed 3/22/2005 has been made of record. Claims 1-22, 24-29 and 32 are pending. Claims 1-16 are withdrawn. Accordingly, claims 17-22, 24-29 and 32 are under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Objections/Rejections: Withdrawn

Specification

Objections to the specification for referencing figures not present in the specification and grammatical errors has been withdrawn in response to amendments to the specification.

Information Disclosure Statement

Applicant has brought to the attention an oversight by the Examiner wherein a translated reference was not considered. The reference not considered was authored by Baba H. (Clinical Calcium, Secretion and Metabolism of PTH/PTHrP, Vol. 5 no. 2). It is made of record that the reference has been considered.

Claim Rejections - 35 USC § 112, first paragraph

Rejections under 35 U.S.C. § 112, first paragraph, for not meeting the enablement requirements because the method was drawn to "preventing" drug-resistant

hypercalcemia is withdrawn in response to amendments to the claims wherein "preventing" was deleted.

Rejections under 35 U.S.C. § 112, first paragraph, for not meeting the enablement and written description requirements because the method was drawn to treating drug-resistant hypercalcemia using at least one "substance" is withdrawn in response to amendments to the claims wherein at least one "substance" was replaced with "anti-PTHrP antibody".

Rejections under 35 U.S.C. § 112, first paragraph, for not meeting the enablement requirements because the method was drawn to treating drug resistant hypercalcemia wherein drug resistance to "at least one of bisphosphonate and calcitonin" is observed has been withdrawn upon further consideration.

Rejections under 35 U.S.C. § 112, first paragraph, for not meeting the enablement requirements because the method was drawn to treating drug-resistant hypercalcemia using at an "anti-PTHrP antibody" has been withdrawn in response to arguments set forth by Applicant and upon further consideration.

Rejections under 35 U.S.C. § 112, first paragraph, for not meeting the enablement and written description requirements because the method was drawn to treating drug resistant hypercalcemia using "an antagonist of the PTHrP receptor" has been withdrawn as a result of amendments and/or cancellation of claims reading on "an antagonist of the PTHrP receptor".

Objections/Rejections: Maintained/New Grounds

Double Patenting

Rejection of claims 17-32, now applied to claims 17-22, 24-29 and 32, for obviousness-type double patenting over copending Application No. 09/720,326 is maintained for the reasons of record in the previous office action (mail date: 09/23/2004).

Applicant has acknowledged the rejection and is considering filing a terminal disclaimer should allowable subject matter be indicated. It is noted that traversal at that time will not be considered timely. Applicant is reminded that overcoming the instant rejection with a terminal disclaimer requires common ownership of the applications.

Claim Rejections - 35 USC § 112, 1st paragraph

Rejection of claims 17-32, now applied to claims 17-22, 24-29 and 32 for not meeting the full scope of enablement requirements under 35 U.S.C. § 112, first paragraph, pertaining to "at least one symptom", "drug-resistant hypercalcemia is resistant to a therapeutic agent for hypercalcemia", and drug-resistant hypercalcemia to a "bone resorption-inhibiting agent, a calcium excretion-promoting agent, an agent for inhibiting intestinal absorption of calcium, and a loop diuretic" is maintained for the reasons of record in the previous office action (mail date: 09/23/2004).

Applicant argues amendments of the claims and teachings in the specification are sufficient to overcome the rejections. Applicant specifically points to pages 5-10 and 12-17 for support. Pages 5-10 and 12-17 teach how to make antibodies, antibody

variants, recombinant antibodies, assays for determining activity, routes of administration, and pharmaceutical preparations. Applicant further argues support for the instant invention through Examples 1-2. Examples 1-2 allegedly teach administration of a humanized antibody derived from clone #23-57-137-1 can decrease blood calcium levels in experimentally induced drug resistant hypercalcemia to bisphosphonate and calcitonin. It is argued that undue experimentation would not be needed to practice the instant invention, citing *In re Wands*. Applicant states, "experimentation needed to determine drug-resistance would not be undue", in reference to rejections based on Applicant only supplying evidence treating drug resistance to a bisphosphonate and a calcitonin.

Arguments have been fully considered, however they are not found persuasive. Applicant has failed to show the instant invention is able to treat any and all symptoms of drug resistant hypercalcemia. "At least one symptom" could encompass a myriad of symptoms ranging from soft tissue calcification to seizures, however the instant specification only discloses the ability to treat two symptoms of drug resistant hypercalcemia, blood calcium quantities and body weight. As such a person of ordinary skill in the art would not be able to make and/or use in the invention as claimed because other possible symptoms, *e.g.* seizures, are not known or do not otherwise logically flow from the instant specification to be treatable with anti-PTHrP antibodies under conditions of drug resistance hypercalcemia.

The claims are also drawn to drug resistance wherein "drug-resistant hypercalcemia is resistant to a therapeutic agent for hypercalcemia". Applicant has

shown the ability of specific anti-PTHrP antibodies to treat drug resistant hypercalcemia wherein drug resistance against selected bone resorption-inhibiting agents is observed. However, there is not support or rationale for the assertion that the instant method would be effective for treating drug resistant hypercalcemia not responsive to "a therapeutic agent for hypercalcemia". Additionally, claim 17 reads on drug resistant hypercalcemia wherein drug resistance to anti-PTHrP antibodies is observed. As such, the instant invention would have no effect since drug resistance encompasses the claimed method of circumventing forms of drug resistant hypercalcemia, *i.e.* using anti-PTHrP antibodies to treat drug resistant hypercalcemia. Furthermore, the different classes of drugs recited in the claims work by different mechanisms of action. For example, what if hypercalcemia is resistant to loop diuretics due to kidney disease? In that case there would be no reason to believe that antibodies to PTHrP would be able to treat hypercalcemia under such conditions. Anti-PTHrP antibodies would not have any effect on pathological conditions related to kidney dysfunction and possible drug resistant hypercalcemia to loop diuretics. Another issue relating drug resistance wherein "drug-resistant hypercalcemia is resistant to a therapeutic agent for hypercalcemia" is that undue experimentation would be needed to determine if the instant method would be effective for treating any drug resistant hypercalcemia

Claims 17-22, 24-29 and 32 are newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims read on treating subjects "susceptible" to drug resistant hypercalcemia. For the claims to be fully enabled under the claimed premise there would need to be adequate teachings or

rationale relating to how the skilled artisan would be able to distinguish susceptible individuals. In other words, Applicant must be able to show they are able to reliably detect what patients will display drug resistant hypercalcemia. Applicant has not shown such predictive measures nor can they be readily obtained through prior art teachings. Therefore, without the ability to reliably predict who would be susceptible to drug resistant hypercalcemia is would not be possible to use the invention as claimed.

For the reasons stated above, as well as those presented in the previous office action, without further guidance, a person of ordinary skill in the art would not be able to practice the invention commensurate in scope with the claims.

Claims 19, 20 and dependent claims 17 and 18 for not meeting the written description requirements under 35 U.S.C. § 112, first paragraph, pertaining to "bone resportion inhibiting agent" is maintained for the reasons of record in the previous office action (mail date: 09/23/2004).

Applicant argues amendment to claims is sufficient to overcome the instant rejections.

Arguments have been fully considered, however they were not found persuasive. A "bone resportion inhibiting agent" as disclosed describes a genus without sufficient distinguishing identifying characteristics so as to permit a person of ordinary skill in the art the ability to predict the genus. Bone resorption-inhibiting agents comprise a broad class of drugs that could have effects on osteoclast activity (bone degradation), osteoblast activity (bone formation), absorption of calcium, excretion of calcium, metabolism of calcium, etc.

For the reason set forth, as well as those presented in the previous office action, the instant disclosure does not support the written description requirements for the methods as claimed.

Claim Rejections - 35 USC § 102

Rejection of claims 17-22, now applied to claims 17-22, 24-29 and 32, as being anticipated by Sato *et al.* under 35 U.S.C. § 102(b) is maintained for the reason of record in the previous office action (mail date: 09/23/2004).

Applicant argues Sato *et al.* do not disclose each limitation of the claims and there is no specific teaching for the treatment of "drug-resistant hypercalcemia". Applicant agrees with the statement that Sato *et al.* teach the progression to drug resistant hypercalcemia after chronic administration of bisphosphonates and calcitonin. Applicant, however, argues there is no direct teaching of methods for treating drug resistant hypercalcemia with anti-PTHrP antibodies. Applicant further argues that Sato *et al.* teach a method of treating hypercalcemia, but not drug resistant hypercalcemia. Applicant states, "it is impossible to predict, whether or not the same antibody is effective in treating drug-resistant hypercalcemia". Finally, Applicant argues the instant method is not inherent from the cited prior art.

Arguments have been considered, however they have not been found persuasive. Sato *et al.* teach that PTHrP is involved in hypercalcemia associated with malignancy and that repeated treatment using calcitonins and bisphosphonates results in decreased efficacy over time, *i.e.* drug resistant hypercalcemia (p. 4 lines 14-23).

Sato *et al.* also teach that since drug resistance occurs as a result of repeated exposure to certain compounds a novel approach may be to use antibodies directed towards PTHrP (p. 4 lines 24-28/p. 5 lines 1-19). The novel approach disclosed by Sato *et al.* is acting through a different mechanism of action than calcitonins and bisphosphonates and therefore the prior art inherently teaches methods of treating drug resistant hypercalcemia by using anti-PTHrP antibodies. Furthermore, the same patient population is being treated, hypercalcemia associated with cancer (see p. 4: lines 24-25 and claims 29 and 32 of the instant application).

As to the statement made by Applicant regarding the predictability of effectiveness as claimed using antibodies disclosed by Sato *et al.*, Applicant is directed to Figure 12. Figure 12 demonstrates neutralizing capabilities of #23-57-137-1, the antibody disclosed in the instant method. Sato *et al.* demonstrate possession of the antibody used in the instant invention and would clearly be effective for treating drug resistant hypercalcemia under experimental conditions presented in the instant specification, as shown by Applicant.

For the reasons set forth the claims remain rejected as being anticipated by Sato *et al.*

Conclusion

NO CLAIMS ALLOWED.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **J. Jason Galvez, Ph.D**. whose telephone number is **571-272-2935**. The examiner can normally be reached Monday through Friday 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback, Ph.D.** can be reached at **571-272-0887**.

The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JJG
6/10/2005

JANET ANDRES
PRIMARY EXAMINER